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HEAD & NECK

Intraoperative frozen section for detection of occult metastasis in clinically N0 neck does not improve outcome in oral cavity carcinomas

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Abstract

Objective The objective of this study was to evaluate the utility of frozen section (FS) in detecting occult nodal metastasis in cN0 OSCC and its impact on regional failure and survival.

Materials and methods Clinical records of patients of OSCC operated from January 2013 to December 2014 were retrospectively reviewed. These patients were divided into two groups—Group A comprised of patients who underwent selective neck dissection (SND) (level III/IV) and FS based completion (level IV ± V); Group B included patients who underwent SND I–III/IV without FS. The sensitivity and specificity of FS in detecting occult metastasis was calculated. The regional failure rates and overall survival (OS) between the two groups were compared.

Results The sensitivity, specificity, PPV (positive predictive value) and NPV (negative predictive value) of FS in detecting occult metastasis were 64.06%, 100%, 100%, and 92.15%, respectively. There was no significant difference in regional failure rates ($p = 0.219$) and OS ($p = 0.08$) between the two groups.

Conclusion FS has a poor sensitivity in detecting occult nodal metastasis. FS-guided neck dissection does not have a significant impact in reducing regional failure or improving OS in clinically node-negative neck in oral cavity carcinomas.

Keywords Frozen section · Occult metastasis · Overall survival · Oral cavity cancer

Introduction

An integral part in the treatment of oral squamous cell carcinoma is surgery. It involves resection of the primary tumor with neck dissection and appropriate reconstruction. Metastasis to the regional neck nodes has been found to be a poor prognostic factor affecting survival [1]. Presence of nodal metastasis determines the extent of neck dissection and the need for adjuvant treatment. Clinically obvious metastatic neck nodes can easily be detected by physical examination and imaging. However preoperative diagnosis of occult nodal metastasis is challenging and elusive to routine diagnostic tools. Intraoperative frozen section analysis of the neck nodes has been used as a modality for detection of occult metastasis and to guide the extent of neck dissection.

Materials and methods

The study was conducted at a tertiary cancer centre to evaluate the utility of frozen section analysis (FS) of neck nodes for clinically negative neck (cN0) in oral cancer patients. The study end points were to determine the sensitivity and specificity of frozen section in detecting occult metastasis and whether FS-directed neck dissection had an impact on regional failure and overall survival. Data of all the oral squamous cell carcinoma (OSCC) patients operated at our hospital from January 2013 to December 2014 were retrospectively retrieved from the electronic medical records. Patients with clinically negative nodes (cN0) who underwent an elective neck dissection were identified. In absence of clear evidence, two Units under Head and Neck Surgery

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Department of our institution routinely use FS as a guide to decide the extent of neck dissection while the remaining third Unit routinely does level I–III/IV nodal clearance in N0 neck. Based on this difference in Unit policies, the patients were retrospectively divided into two groups. Group A comprised of patients who underwent levels I–III/IV neck dissection with FS analysis of neck nodes followed by completion neck dissection (level IV ± V) based on FS reports. A subset of patients in this group underwent level IIB clearance based on the FS analysis of level IIA nodes. Group B comprised of patients who underwent routine level I–III/IV neck dissection without FS of nodes.

As per our institutional protocol, frozen sections were performed by an experienced pathologist assisted by a senior resident and a trained technologist. Lymph nodes larger than 1 cm were bisected and both halves were evaluated. Smaller nodes were processed *en bloc*. Sections were cut at − 20 °C using a cryostat. As a protocol, for each frozen block, two sections—one stained with 1% toluidine-blue and the other stained with rapid haematoxylin and eosin—were evaluated for metastasis under the microscope. Frozen report was immediately conveyed telephonically to the operating surgeon. Staining procedure followed in each case was as follows: toluidine-blue: slide was dipped in 1% toluidine-blue solution for 1 min, washed and mounted in glycerine. Rapid haematoxylin and eosin: slide was dipped in haematoxylin for 1 min. After washing, one dip in 1% acid alcohol for differentiation followed by 'blueing' under tap water for 2 min. Thereafter, a dip in 1% aqueous eosin was given followed by mounting. Information regarding clinico-pathological factors and survival was obtained from electronic medical records (Table 1). As per our institutional policy, in the absence of any adverse factor depth of invasion great than or equal to 1 cm received post-operative radiotherapy. Patients who did not follow up after surgery were excluded from the survival analysis. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of FS in determining occult nodal metastasis were calculated. The impact of FS on regional failure was calculated by comparing the incidence of regional failure between the two groups using Chi square test. The overall survival (OS) was defined as the period from the date of surgery to the date of death from any cause or last follow-up whichever was earlier and was calculated using Kaplan–Meier method. The difference in OS between the two groups was analysed using Log rank test. The clinico-pathological profiles were compared between the two groups using Chi square test. All statistical tests were two-sided, and a p value of 0.05 or less was considered statistically significant. Analysis was performed using IBM Statistics SPSS version 20.

Table 1 Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of frozen section (FS)

		Nodal metastasis present	Nodal metastasis absent
FS positive		41	0
FS negative		23	270
Sensitivity-64.06%	Specificity-100%	PPV-100%	NPV-92.15%

Results

A total of 1110 patients of OSCC were operated in the mentioned time frame. Of these, 684 patients were found to have a clinically negative neck (cN0). Fifty one cN0 patients did not undergo a neck dissection and were excluded from the analysis. The rest 633 patients formed the study population. Group A (FS group) comprised of 334 (52.76%) patients and Group B (no FS group) had 299 (47.23%) patients. Six patients did not follow up after surgery (five in Group A and 1 in Group B) and were excluded from analysis. Thus the impact of FS on survival and regional failure was analysed for 627 patients (329 in Group A and 298 in Group B). Male patients (82.5%) dominated the study population. The median age was 51 years (range 19–81 years). The median follow-up was 36 months (range 1–57 months); 37 months in Group A and 35.5 months in Group B. About 70% patients had cancers of the bucco alveolar complex while the rest 30% comprised of cancers of the oral tongue and floor of mouth. At the time of analysis, 445 patients (71.0%) were alive without disease, 50 were alive with disease (7.9%), 126 patients (20.1%) had died due to disease and 6 patients (1.0%) had died due to other causes. Overall, 495 patients (78.9%) were alive at the time of analysis. In the entire cohort, the site of failure was only local in 90 (14.4%) patients, only regional in 38 (6.1%) patients, both locoregional in 18 (2.9%) patients and distant in 29 (4.6%) patients. Overall occult nodal metastasis was found in 117 (18.48%) patients on histopathology [64 patients (19.16%) in Group A; 53 patients (17.72%) in Group B)]. In Group A, FS could detect occult metastasis in 41 (64.06%) patients (true positives) and failed to do so in the rest 23 (34.94%) patients (false negatives). Out of the 23 false-negative results, 19 had sampling error in detecting occult metastasis. None of the patients had false positive-results on frozen section. The sensitivity, specificity, PPV and NPV of FS in detecting occult nodal metastasis were 64.06%, 100%, 100% and 92.15%, respectively (Table 1). Within Group A, 230 patients had clinical stages I and II (cT1 + T2 cN0) cancers. Amongst these patients, 44 (19.13%) harboured occult metastasis detected on histopathology. Frozen section could detect occult metastasis in 30 patients of this subgroup—the sensitivity, specificity, PPV and NPV being 68.18%, 100%, 100%, and 93%, respectively (Table 1). The distribution pattern of clinico-pathological and treatment-related factors between the two groups are depicted in Table 2. The average number of nodes dissected per neck dissection was 27.04 in the entire cohort (27.57 in Group A and 26.32 in Group B). The two groups were fairly balanced in all the factors except for depth of invasion and adjuvant treatment received. A significantly more number of patients in Group A had depth of invasion ≥ 1 cms as compared to Group B [172 (52.3%) in Group A and 130 (43.6%) in Group B; $p=0.03$]. Similarly more patients in Group A received adjuvant therapy [238 (72.3%) in Group A and 186 (62.4%) in Group B; $p=0.008$]. Overall, regional failure (regional + loco regional failure) was seen in 56 (9.0%) patients. There was no significant difference in the incidence of regional failure between the two groups although Group A had fewer regional failures [25 (7.6%) in Group A; 31 (10.4%) in Group B, $p=0.219$] (Table 3). The estimated 2 and 5 years survival in the entire study population were 82.0% and 74.8%, respectively. The effect of various clinico-pathological factors on overall survival is depicted in Table 4. Occult nodal metastasis significantly affected survival in both univariate ($p=0.00$) and multivariate ($p=0.024$) analysis. There was no significant difference in survival between the two groups although Group A patients had a trend of better survival [estimated 2 and 5 years OS in Group A were 84.2% and 77.0%, respectively; the corresponding figures in Group B were 79.6% and 72.5%, respectively; $p=0.08$] (Fig. 1). In Group A, out of the 41 patients found to have occult nodal metastasis on FS, 37 underwent completion neck dissection based on the results of FS. One patient was lost to follow-up. The incidence of regional failure was compared between the patients who underwent completion neck dissection and those who did not. Regional failure was found to be higher in the group who underwent completion neck dissection [6/36 patients (16.6%)] as compared to those who did not undergo completion [50/591 patients (8.4%)]; the

Table 2 Distribution of clinico-pathological and treatment factors across the two study groups

	Group A $N=334$ (52.76%) (FS done)	Group B $N=299$ (47.23%) (FS not done)	*p* value
Site			
Tongue and FOM	106	86	0.416
Bucco alveolar complex	228	213	
Laterality of neck dissection			
Unilateral	282	256	0.676
Bilateral	52	43	
T stage			
pT1 + T2	230	207	0.920
pT3 + T4	104	92	
Grade			
WD	79	82	
MD	200	177	0.384
PD	55	40	
PNI			
Present	61	42	0.151
Absent	273	257	
LVS			
Present	2	5	0.197
Absent	332	294	
Microscopic margins			
Free	318	273	0.099
Close	11	21	
Involved	5	5	
Number of nodes dissected per neck dissection (mean)	26.32	27.52	0.247
Extra capsular spread			
Present	41	41	0.591
Absent	293	258	
Occult nodal metastasis			
Present	64	53	0.642
Absent	270	246	
Adjuvant treatment			
Received	241	186	0.008
Not received	93	113	

Table 3 Comparison of regional failure between the Groups A and B

	Group A	Group B	*p* value
Regional failure	25 (7.48)	31 (10.36)	0.202
No regional failure	309 (92.51)	268 (89.63)	

Table 4 Clinico-pathological factors affecting overall survival

Factor analysis	Univariate analysis *p* value	Multivariate *p* value
Subsite	0.611	–
T stage	**0.000**	**0.002**
Occult nodal positivity	**0.000**	**0.049**
Grade	**0.000**	**0.013**
PNI	**0.000**	**0.006**
LVS	0.358	–
Microscopic margins	**0.018**	0.202
Adjuvant treatment	**0.000**	0.417
Frozen section neck nodes	0.091	–

Statistically significant values are in bold ($p < 0.05$)

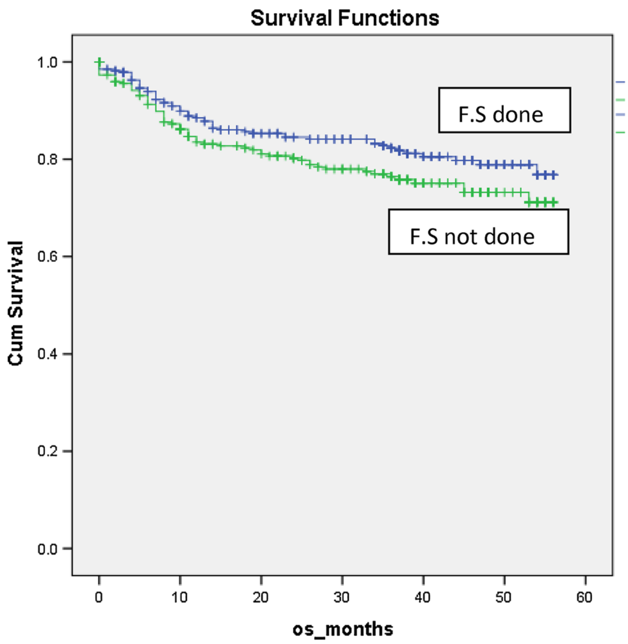

Fig. 1 Effect of intraoperative frozen section-guided neck dissection on overall survival

Table 5 Regional failure in patients undergoing completion neck dissection versus observed based on FS reports

	Group A		*p* value
	Completion neck dissection done (%) $N=37$ (11.07)	Completion neck dissection not done (%) $N=295$ (88.32)	
Regional failure	6 (16.21)	19 (6.44)	0.095
No regional failure	31 (83.78)	276 (93.55)	

difference however did not achieve statistical significance ($p=0.094$) (Table 5). Considering higher incidence of occult metastasis in the neck-negative advanced oral cavity cancers, it was hypothesized that this group would benefit from frozen section of nodes. Therefore, subgroup analysis was done for advanced T (T3 and T4)-stage oral cavity cancers. There was higher (19.9%) occult metastasis in this group as compared to early-stage (17.7%) oral cavity cancers but it was not statistically significant. 14.4% of the Group B had recurrence in neck as compared to 8.8% of Group A. All other risk factors including ECS (extracapsular spread), PNI (perinodal extension), LVI (lymphovascular invasion) were comparable in both groups. However, when we compared the survival in those patients who underwent completion neck dissection after frozen section as compared to those without, there was no significant difference in the outcome of such patients. Thus, negating the role of frozen section for nodes even in advanced node-negative oral cavity cases.

Discussion

The treatment of OSCC is primarily surgery with or without adjuvant therapy. The role of elective neck dissection in improving overall and disease-free survival even for early oral cancers (cT1, T2 N0) has been comprehensively established [2]. The extent of neck dissection depends on the site of the primary tumor, presence of metastatic neck nodes and the nodal stations involved. Levels I–III selective neck dissection is the standard surgery for a cN0 neck in OSCC [3]. It serves both as a diagnostic and therapeutic tool. The incidence of occult nodal metastasis in oral cancers ranges widely from 23.7 to 42% [1] and depends mainly on the site and depth of invasion of the primary tumor [4–7]. Occult nodal metastasis has been found to be a poor prognostic factor affecting survival [1]. Our findings were similar with occult nodal metastasis adversely affecting OS in both univariate ($p=0.00$) and multivariate analysis ($p=0.049$) (Table 4). Preoperative diagnosis of occult metastasis is difficult by routine imaging procedures. USG- and USG-guided FNAC have been conclusively found to have a poor sensitivity in diagnosing occult neck nodal metastasis [8, 9]. Contrast-enhanced CT scans, MRI and PET scans have similar diagnostic accuracy with sensitivity ranging from 52 to 66% [9]. Sentinel node biopsy (SNB) has evolved as a diagnostic tool for evaluation of occult nodal metastasis in cN0 neck [8, 10, 11]. Although this procedure has been adopted as an alternative to selective neck dissection by many centers especially in Europe, we do not use SNB as a routine diagnostic tool for cN0 OSCC. Thus we evaluated the diagnostic role of frozen section for intraoperative detection of occult nodal metastasis and its prognostic significance on regional failure and survival. This study was planned based on the results of a previous study from our institution which evaluated the role of frozen section for margin assessment and detection of occult metastasis in tongue cancer patients [12]. In that study, one third of the patients with clinically negative neck were found to harbour occult metastasis on FS analysis. Of the patients who underwent additional nodal dissection based on FS results, 11% had metastasis in lower neck nodal levels (level IV ± V) on final histopathology. However, FS failed to diagnose 7% of patients with occult metastasis (false negatives). Thus, the benefit of FS for detecting occult nodal metastasis remained shadowed by a high false-negative rate. We planned to further explore the utility of FS for neck nodes using a completely different database. The sensitivity, specificity, PPV and NPV of FS in detecting occult nodal metastasis were 64.06%, 100%, 100% and 92.15%, respectively. The poor sensitivity was due to the high false-positive rates (6.88%). Most of the false-positive reports resulted out of sampling errors. Although various anatomical, surgical and pathological factors affect lymph nodal yield, most studies report an average number of nodes dissected in a supra omohyoid neck dissection to be 16–19 nodes. Performing a FS analysis on so many nodes apart from being a time consuming, costly and laborious process carries a high risk of sampling error of missing out occult metastatic nodes. Literature is limited focusing on the role of FS in determining occult nodal metastasis in OSCC. Similar to our findings, other studies have reported a poor sensitivity (42–73%) with a high specificity (100%) [13–18]. The previous study from our institution also found a false-negative rate of 7% in tongue cancers [12]. A study from Canada evaluating the role of FS in detecting occult central compartment nodes in thyroid cancers found its sensitivity, specificity, PPV and NPV to be 68.8%, 100%, 100%, and 94.4%, respectively [19] which was almost similar to our results. In view of high false-negative rates and a poor sensitivity, FS does not stand out to be a good diagnostic tool for detection of occult cervical nodal metastasis. In our study, frozen section-directed neck dissection did not significantly improve the neck failure rates or the overall survival even though most of the confounding factors that could affect survival were evenly distributed between the two groups (Table 2). An elective level III neck dissection without FS (group B) which is expected to decrease the cost, surgical time and manpower needs had similar oncologic outcomes. The non-significant benefit in survival in Group A may have resulted due to a significantly more number of patients receiving adjuvant treatment ($p = 0.008$) in that group. A higher number of patients in Group A with depth of invasion ≥ 1 cms ($p = 0.03$) could have resulted in the discrepancy between the two groups regarding adjuvant treatment (our institutional policy is to give adjuvant radiation in tumors with depth of invasion ≥ 1 cms with no other adverse pathological features). Our study did not find a benefit of completion neck dissection in reducing regional failures. In fact, regional failures were more in patients who underwent completion neck dissection; the difference, however, was not significant. These results were reproduced even in advanced T-stage oral cavity cancer in which higher occult nodal metastasis was present. Thus, an oncologic benefit of levels VI/V clearance in the setting of clinically N0 neck with occult metastasis remains questionable with definitely higher chances of functional morbidity. This hypothesis is, however, confounded by a higher number of occult nodal metastasis in the group who underwent completion neck dissection and a discrepancy in sample size. It would have been interesting to compare the neck failure rates in Group A patients who underwent a completion neck dissection with those who did not undergo further neck dissection following the detection of occult nodal metastasis on FS; however, the number of patients in the latter group was very less (four patients) for meaningful analysis. Though our study had majority of buccoalveolar complex cancers, we also had 30% (192) oral tongue complex cancers. Thus, results of this study may be extrapolated to regions which had higher rates of oral tongue cancers.

Our study being a retrospective one had its own limitations. Data on the pattern of regional failure were also not available in our database. However, to our knowledge, this study is the first one to intricately assess the role of frozen section analysis of neck nodes in cN0 oral cancer patients in relation to regional failure and survival with a fairly decent follow-up. Furthermore, it consolidates the finding of poor sensitivity of FS in detection occult cervical nodal metastasis.

Conclusions

Frozen section is not a sensitive tool for intraoperative detection of occult cervical nodal metastasis. The cost, time and expertise required do not translate into a meaningful clinical benefit in terms of regional failure and overall survival for clinically node negative in oral cavity squamous carcinomas.

Compliance with ethical standards

Conflict of interest None of the authors have any conflict of interests to declare.

Research involving human participants and/or animals This is a retrospective study, hence, does not require any intervention on any human participants and/ or animals. The data were obtained from electronic medical records (EMR) after obtaining appropriate permissions.

Informed consent Since this is a retrospective study waiver of consent was taken from the Institute's Ethics Review Board (IRB).

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